

Cell Communication

Multicellular organisms can be thought of as behaving as a community

- Neighbors carry on private conversations.
- Messages are sent from distant sites to the individual.
- Public announcements are made to the whole community population.
- Alarms are rung when danger is present.

Just as in a family or community, a breakdown in communication can have detrimental effects. Many metabolic disorders and cancers are a result of malfunctioning communication among cells.

General Principles of Cell Signaling

Signal transduction involves the conversion of signals from one form to another in a cell. Eventually, a response occurs as a result of the initial signal.

Oral Instructions → Text → network e-mail → voice → Action

Chemical signals can be proteins, amino acids, peptides, nucleotides, steroids, gases. Most signals are hydrophilic so are unable to pass through membrane (proteins, a.a., peptides, etc.) Some signals are hydrophobic and are able to pass through the membrane to begin a response (steroid hormones). These signals are produced by the **signal cell** and detected by a **receptor protein** on a **target cell**.

- 1) The most general form of signaling involves a *signal produced by the endocrine system* called a hormone. **Hormones** communicated to cells over some distance, produced at one site and acting on another. They are transported through the bloodstream in animals or the sap of plants.

General Public Address Announcement.

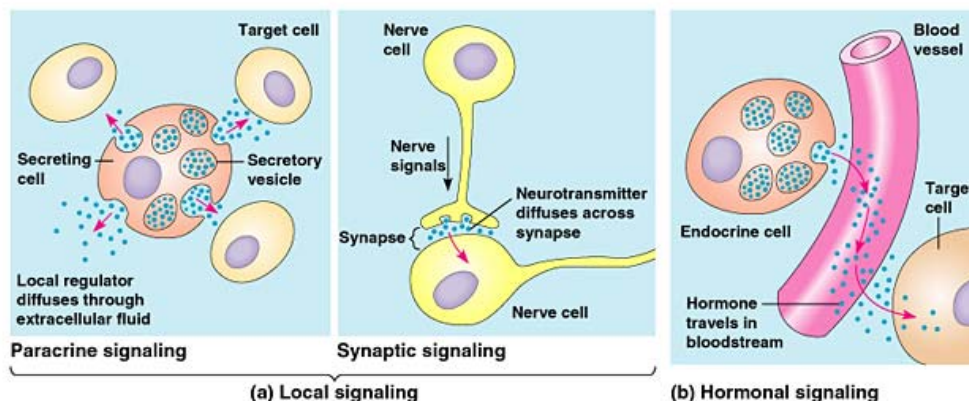
More localized communication takes place through→

- 2) _____:
 ➤ One cell secretes the signal into the extracellular fluid and it acts on a nearby target cell.
 ➤ Ex. Histamines in inflammatory response, PDGF, NGF, Nitric oxide

Phone Call to the Classroom

- 3) _____:
 ➤ Nerve cell (_____) release its signals (_____) into a space. Neurotransmitters diffuse across the space to a neighboring neuron or muscle cell and activate it. This can cause a change in the target cell to effect some change (muscle) or carrying on the signal in the form of a nerve impulse.
 ➤ Messages can be delivered over great distances but occur through private lines at a rapid rate (100 m/sec).

Cell Phone in your backpack.



- 4) The most specific/direct form of communication involves cell-cell communication by _____.
 ➤ Does not require the release of secreted molecules.
 ➤ Signaling molecules in plasma membrane of one cell bind to receptors embedded in the adjacent cell.
 ➤ Can also take place between _____ and _____.

Face to Face Conversation.



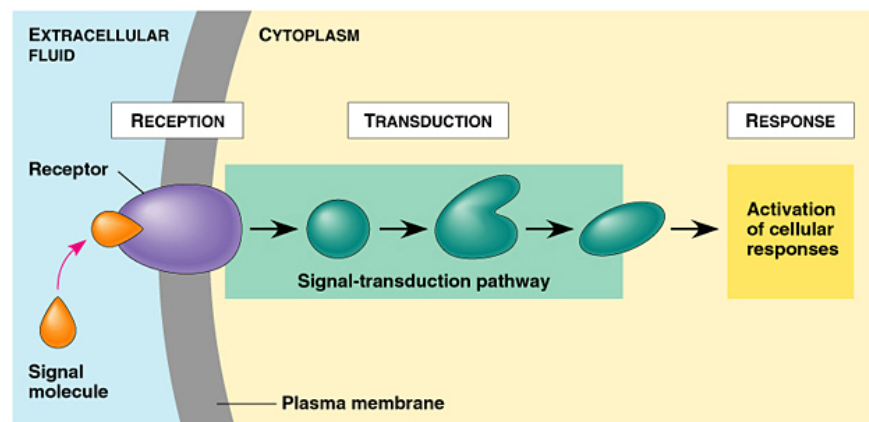
General Stages of Cell Signaling

- ✓ Cells must respond selectively to the hundreds of different signaling chemicals that it is exposed to. This ensures that processes occur in the correct cells, at the right time and in proper coordination with other cells.
- ✓ Cells may respond to a signal differently depending on the intracellular relay system that is intact within the cell.
 - ✓ Ex. One cell may contract (skeletal muscle), one cell may relax (heart) and one cell may secrete (salivary gland) all as a response from the same chemical signal.

Components of a Signaling System

- Signal molecule binds to specific cellular protein called a **receptor** that is located on the target cell.
- Signal molecule is a _____ (molecule that binds to another). Ex. Hormones (adrenaline, estradiol, insulin, glucagon); Local mediators (PDGF, NO, NGF); Neurotransmitters (acetylcholine).
- Receptors are usually activated by only one signaling molecule and function to take an extracellular signal and convert it to an intracellular signal.
- Most signal receptors are plasma membrane proteins (*G-protein-linked receptor, Tyrosine kinase receptor, Ion-channel receptors*)

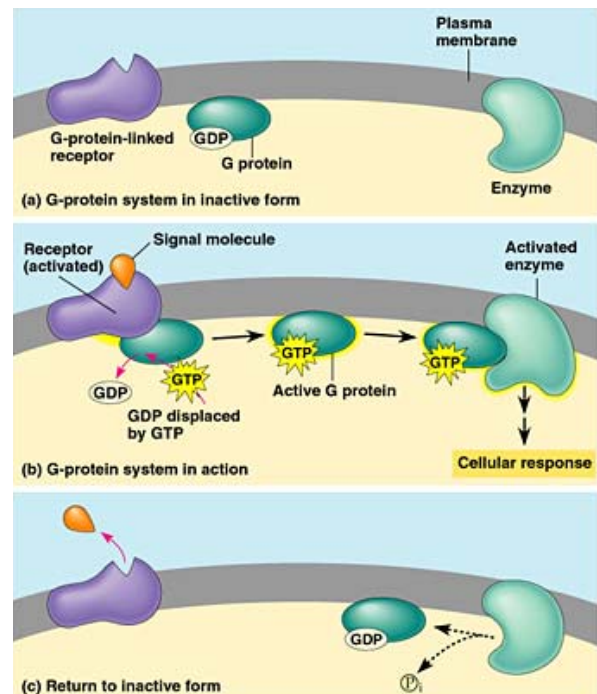
- _____:
- Ligand causes a conformation change in receptor protein. This causes a series of responses in the cell that convert the original signal into cellular responses (signal transduction).



- _____:
- Intracellular signaling molecules can eventually cause an enzyme to become activated or for the expression of gene to begin/end.

Plasma Membrane Proteins

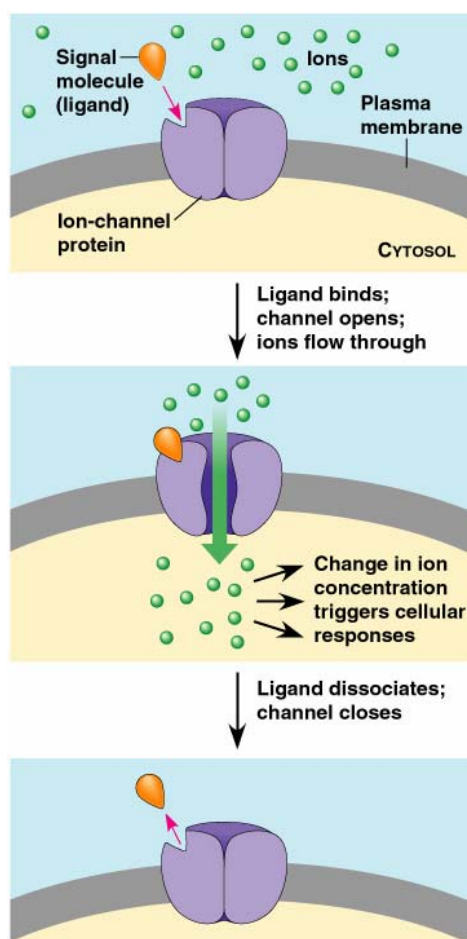
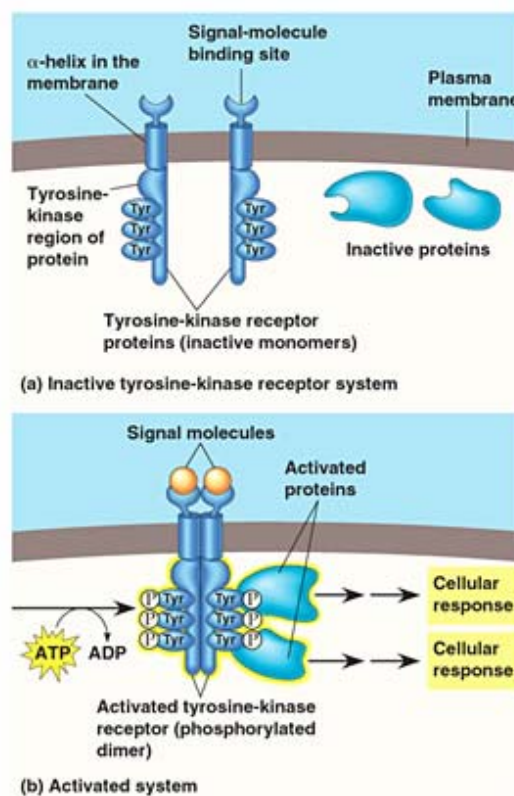
- a) Largest family of receptors.
- b) Signaling molecules can be _____
- c) _____
Single polypeptide threaded back and forth across membrane 7 times (aka. 7-pass transmembrane receptor proteins)
- d) When a signal molecule binds to G-protein-linked receptor a change in conformation occurs enabling it to interact with a _____ on the intracellular side of the membrane.
 - (1) G-proteins are made of 3 protein subunits that are separate from the receptor complex.
 - (2) G-proteins are activated when a GTP (guanosine triphosphate) is bound to them. Activated G-proteins are able to diffuse along the membrane to find their target proteins.
- e) Activated G-proteins bind to other proteins (usu. enzymes) that begin the signal transduction. The longer they are bound, the stronger and more prolonged to relayed signal.
- f) G-proteins can be deactivated by the hydrolysis of GTP to GDP. (G-protein has intrinsic GTPase activity). Once GTP is replaced, the G-protein is inactive and ready to be activated by another signaling molecule.
- g) Defects in turning on and turning off G-Protein-linked Receptors linked to metabolic disorders and disease.



(Enzyme-linked Receptors)

- Important in _____.
Primarily role as growth factor receptor.
- Cytoplasmic side of receptor (tyrosine-kinase domain/region) acts as an enzyme (instead of interacting with another protein i.e. G-protein).
- Switched on by ligand on the extracellular side of membrane. Ligand causes binding of T-K Receptor sub-units to form dimer.
- Cytoplasmic side of receptor becomes _____ by ATP.
- Other cellular proteins (10 – 20) interact with phosphorylated domain of T-K receptor. These then become activated and can initiate numerous transduction systems.
- Termination of signaling process occurs when *protein phosphatase* removes phosphate groups off of proteins. Tyrosine domains lose their phosphates and are no longer active. Activated receptors can also be brought into cell by endocytosis and destroyed with lysosomes.

Activated proteins in T-K domains may activate still other proteins, transmitting the signal onward. One of these proteins, **Ras**, is important in cell growth. Activation of **Ras** is one step in causing cell division. Why is all this important....About 30% of human cancers have mutations in **Ras genes**!



- Serve for rapid transmission across _____ in the _____ system.
- Responsible for the conversion of a chemical signal (neurotransmitter) from outside to an electrical signal inside the membrane of neurons.
- Binding of ligands causes conformation change in channel that allows specific ions to flow (Na^+ , K^+ , Ca^{2+} , Cl^-).
- Once these channels are open, their movement is determined by electrochemical (*remember, concentration and charge*) gradients

G-protein linked receptors and Tyrosine-kinase receptors function to transmit signals into the cell in the form of relay systems formed from intracellular signaling molecules inside of the cell.

These signaling molecules generate other signals or receive a signal in one part of the cell and move to another to have some effect.

Signaling proteins act as Molecular Switches!

A common mechanism used to turn on a protein is with the addition of a phosphate group from ATP.

_____ phosphorylate proteins that are then able to begin operation in some pathway. The proteins act as switch proteins that have been turned to the On Position.

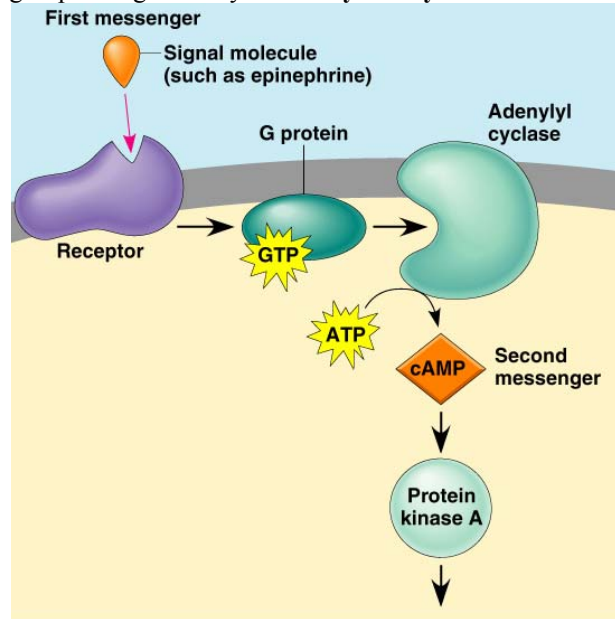
In order to stop the transduction pathway, the initial signal molecule must be removed from the receptor. Then a protein phosphatase removes the phosphate group from the activated protein, turning it off.

Not all components of a signal transduction pathway are proteins. Some signaling systems rely on small, non-protein water soluble molecules or ions. These molecules act as secondary messengers, taking information from the primary messenger (initial signal ligand) and relaying it through the pathway.

Second Messengers

1) Cyclic AMP

- Formed from ATP through the removal of 2 phosphate groups using the enzyme **Adenylate Cyclase**.
- Water soluble so it can move easily throughout the cell.
- Messengers (*adrenaline, epinephrine*) bind to a G-protein linked receptors and activate G-protein complex.
- Activated G-protein activates the adenylate cyclase initiated the conversion of ATP present in the cell to cyclic AMP.
- Cyclic AMP exerts effects within cell by activating the enzyme _____.
- The activation of protein kinase-A causes other phosphorylation events to occur very rapidly. Activating cAMP production can cause rapid effects:
 - ✓ Glycogen breakdown in skeletal muscle to be used for energy,
 - ✓ Fat breakdown in adipose tissue to fatty acids for energy use,
 - ✓ Increase in heart rate and force of contraction.
 - ✓ These responses are part of the Fight or Flight response initiated by a release of adrenaline by adrenal glands.

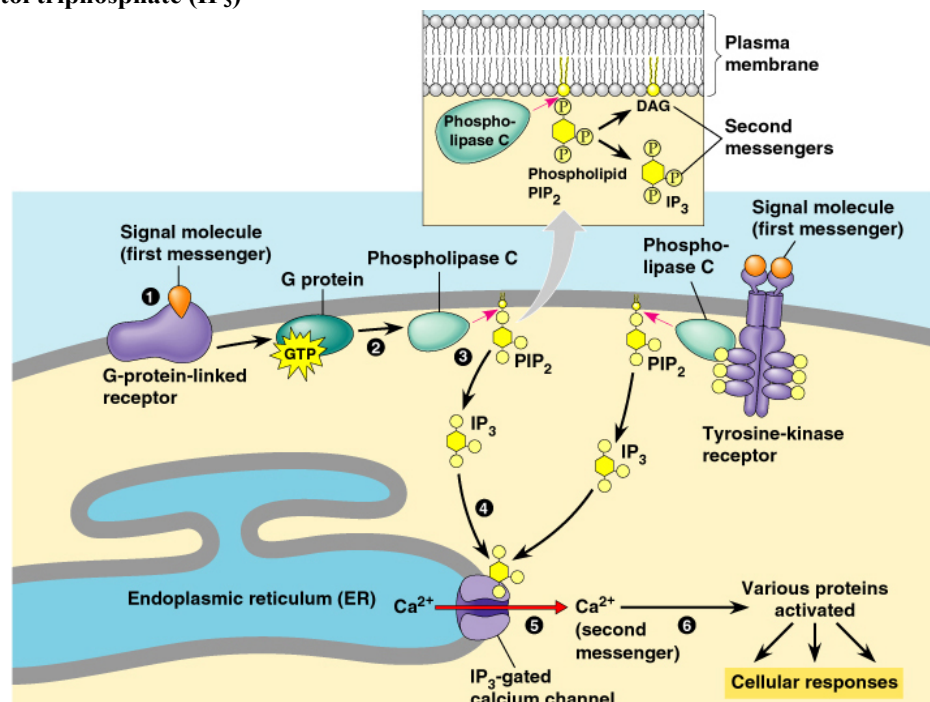


- Other responses are slow, as in the control of gene expression (Figure 15-21).

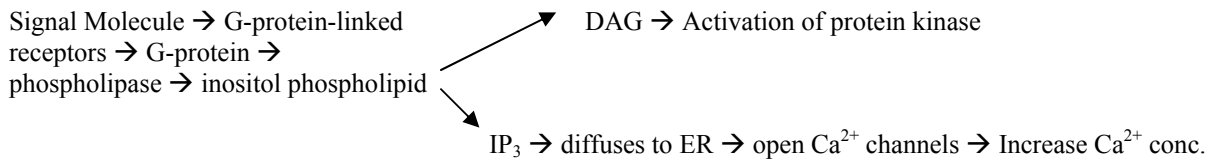
Hormone → G-protein-linked receptor → G protein → adenylate cyclase → cAMP → protein kinase-A → gene regulatory protein → gene transcription altered

2) Calcium ions (Ca^{2+}) and inositol triphosphate (IP_3)

- ✓ Calcium ions play an important role in processes such as muscle contraction, neurotransmitter release by neurons, the growth of cytoskeleton, and the beginning of development of an egg that has been fertilized by a sperm.
 - ✓ Calcium ions are stored in high concentration in the ER (actively pumped into ER from cytosol) and are released when the proper signal has been detected.
- Calcium ions can enter a cell through gated ion channels.
 - Neurotransmitters bind to channel proteins and the flow of ions occurs. This changes the electric potential of the cell across the membrane



- 2) Calcium ions can also be added through the **Inositol triphosphate** (IP_3) pathway (above figure).
- Ligand binds to receptor causing a conformation change.
 - The enzyme **phospholipase [C]** acts on a membrane **inositol phospholipid** (phospholipid with a sugar [inositol] attached). The lipid is hydrolyzed to form two molecules; inositol 1,4,5-triphosphate (**IP_3**) and diacylglycerol (**DAG**).
 - IP_3 leaves the plasma membrane and diffuses to the ER where it binds to and open Ca^{2+} channels in the ER membrane.
 - The concentration of Ca^{2+} increases in the cytosol.
 - DAG helps to activate another protein kinase which can then be used to phosphorylate other proteins.



Signal Transduction Pathways are a means for a cell to:

- ❖ Relay signals from one cell to the cytoplasm of another cell.
- ❖ _____ a signal by allowing a few extracellular signals to evoke an increased production of secondary messengers.
- ❖ _____ the signal by causing a pathway to diverge and be relayed into a number of different targets.
- ❖ Control _____ and _____ by interfering with any of the steps through mutations, intercellular signals and extracellular signals.
- ❖ Produce a signal that is recognized by only a specific group of cells with the appropriate receptors.
- ❖ Rapidly respond to changes (fight/flight, food and smell, photoreceptors in eye)